Role of Acid Sphingomyelinase Knockout Mice in Protection Against Hyperhomocystenimia Induced Glomerular Injury

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Background

- Hyperhomocystenemia is known as a critical pathogenic factor in the progression of end stage renal disease (ESRD) and in the development of cardiovascular complications related to ESRD.

- Chronic elevations of plasma Hcys levels induce proteinuria, mesangial expansion and glomerulosclerosis.

- Elevated Hcys levels increase *de novo* ceramide synthesis in rat mesangial cells. This increased ceramide production enhances NADPH oxidase activity.

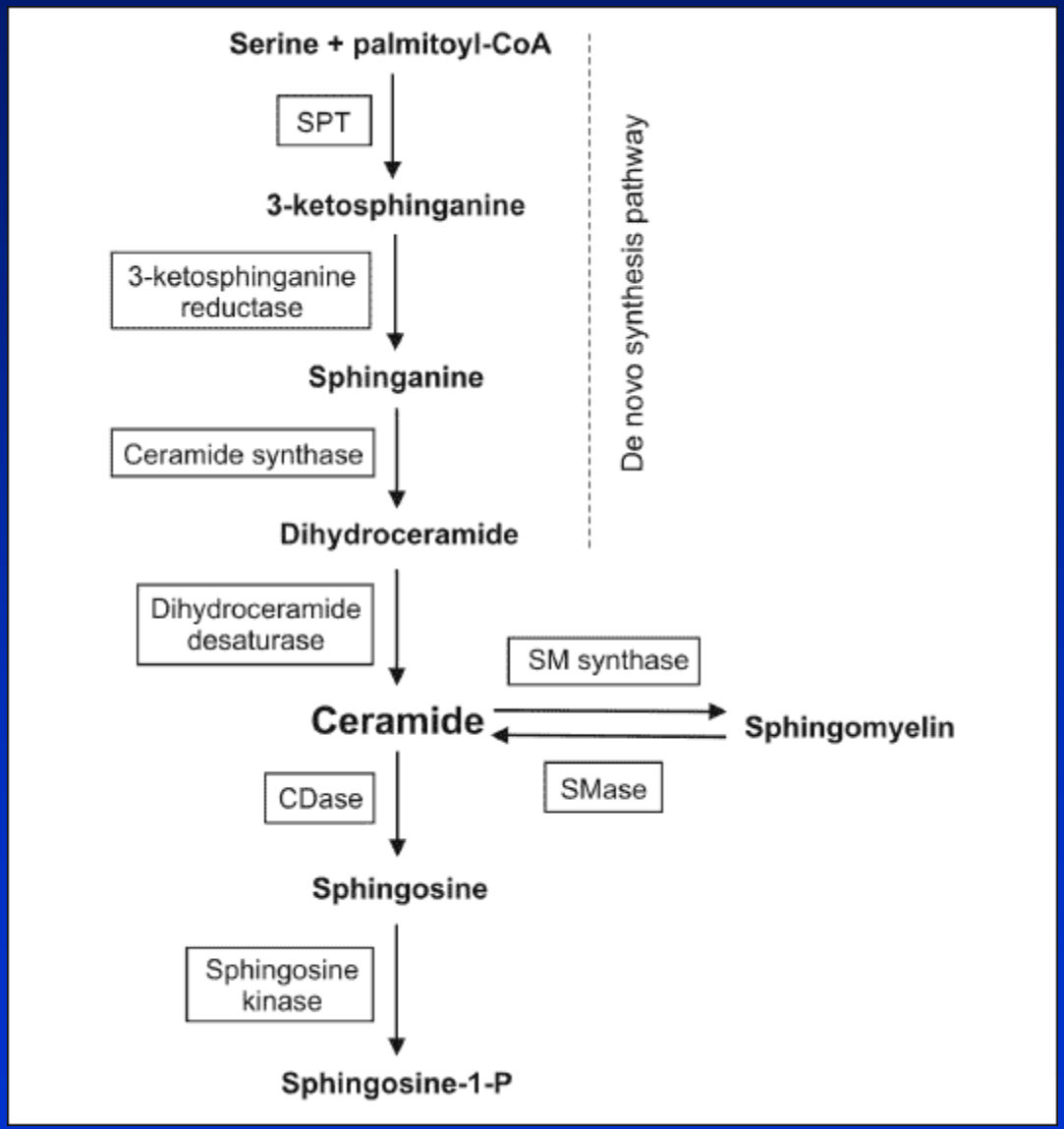
- Increased NADPH oxidase activity generates superoxide production and ultimately causes glomerular injury.

- However, nothing is known about hyperhomocysteinemia induced glomerular injury on mice lacking the acid sphingomyelinase gene.

Hypothesis

To explore the role of acid sphingomyelinase and NAD(P)H oxidase in the development of hHCys-induced glomerular injury in ASM mice

Biosynthesis of Ceramide



FF Diet

↓

↑hHcy

↓

ASM/Ceramide ↑

↓

LR/platform

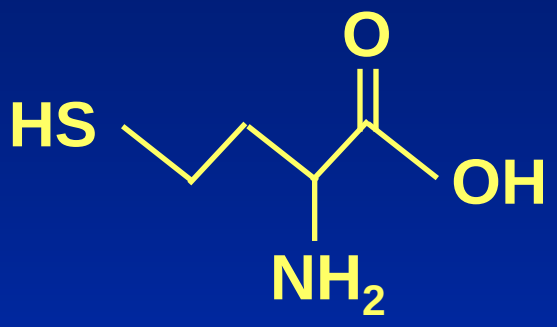
↓

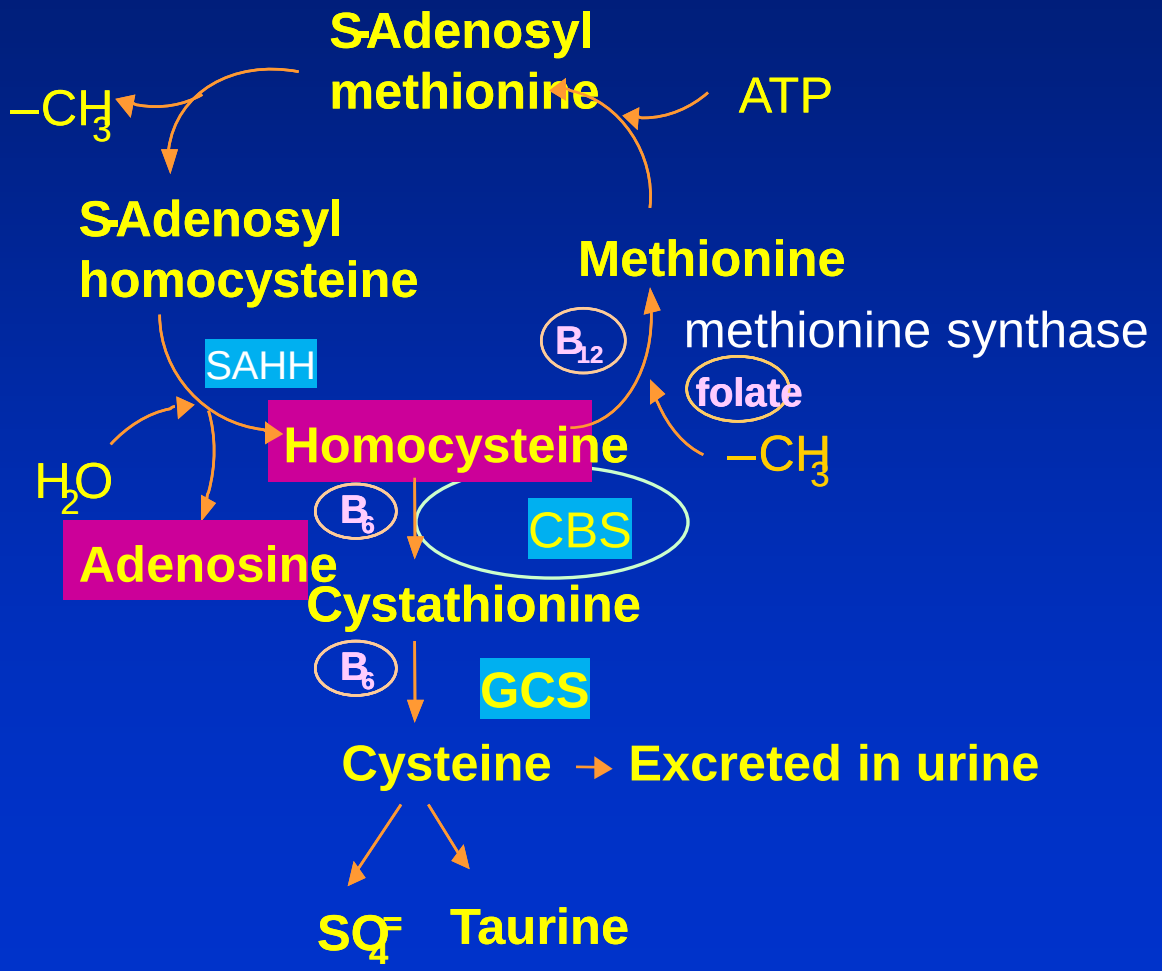
NOX/$O_2^{\cdot-}$ ↑

↓

Glomerular Injury

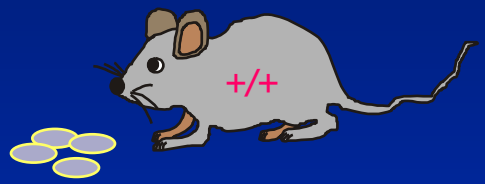
Homocysteine



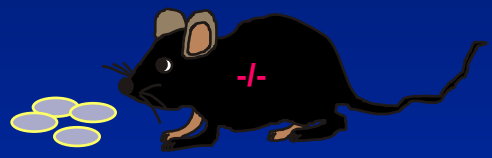


Animal Model

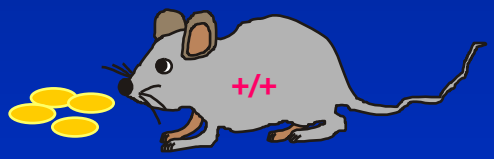
8-weeks old ASM mice



Control diet



Control diet

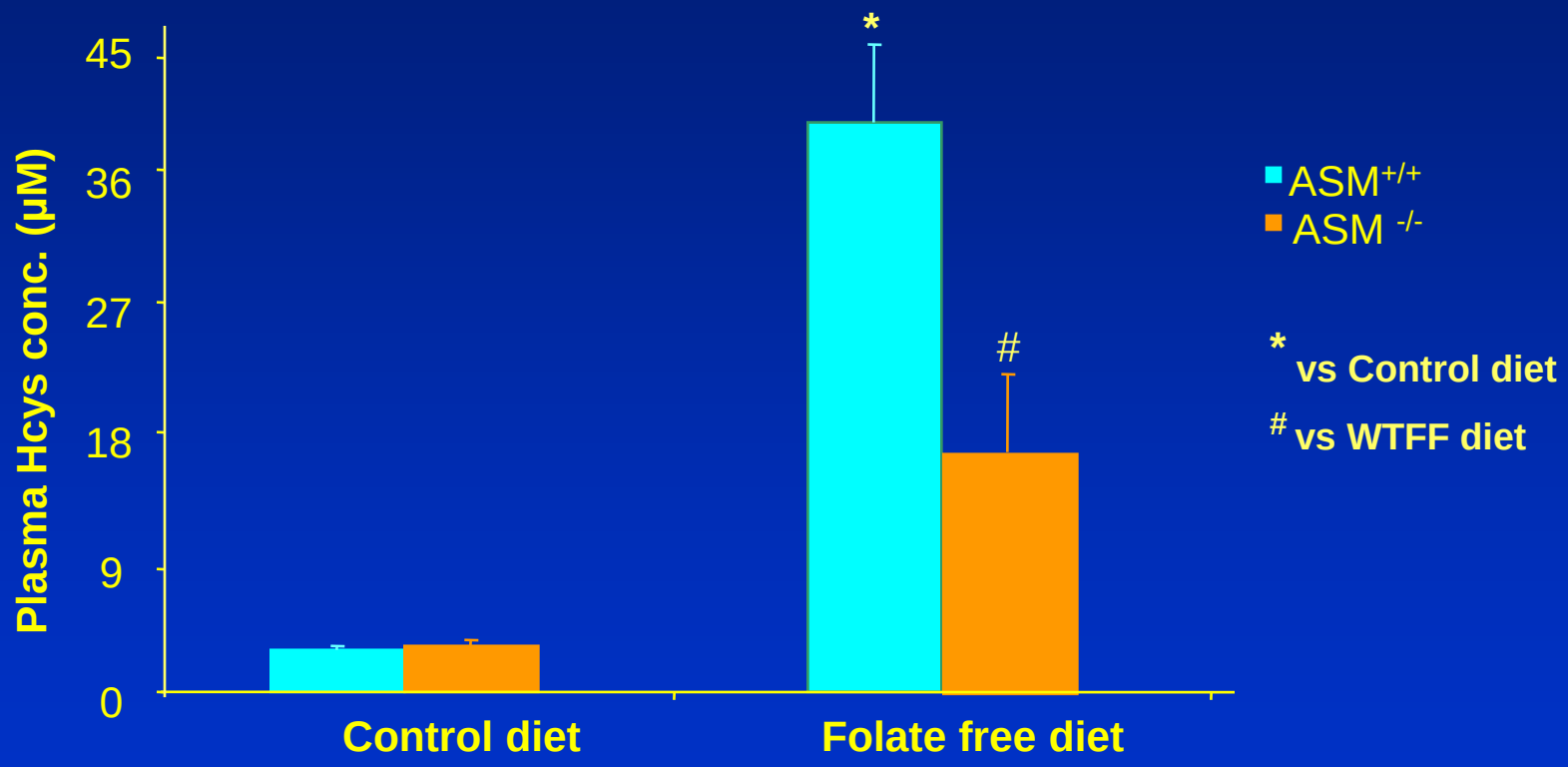


Folate free diet

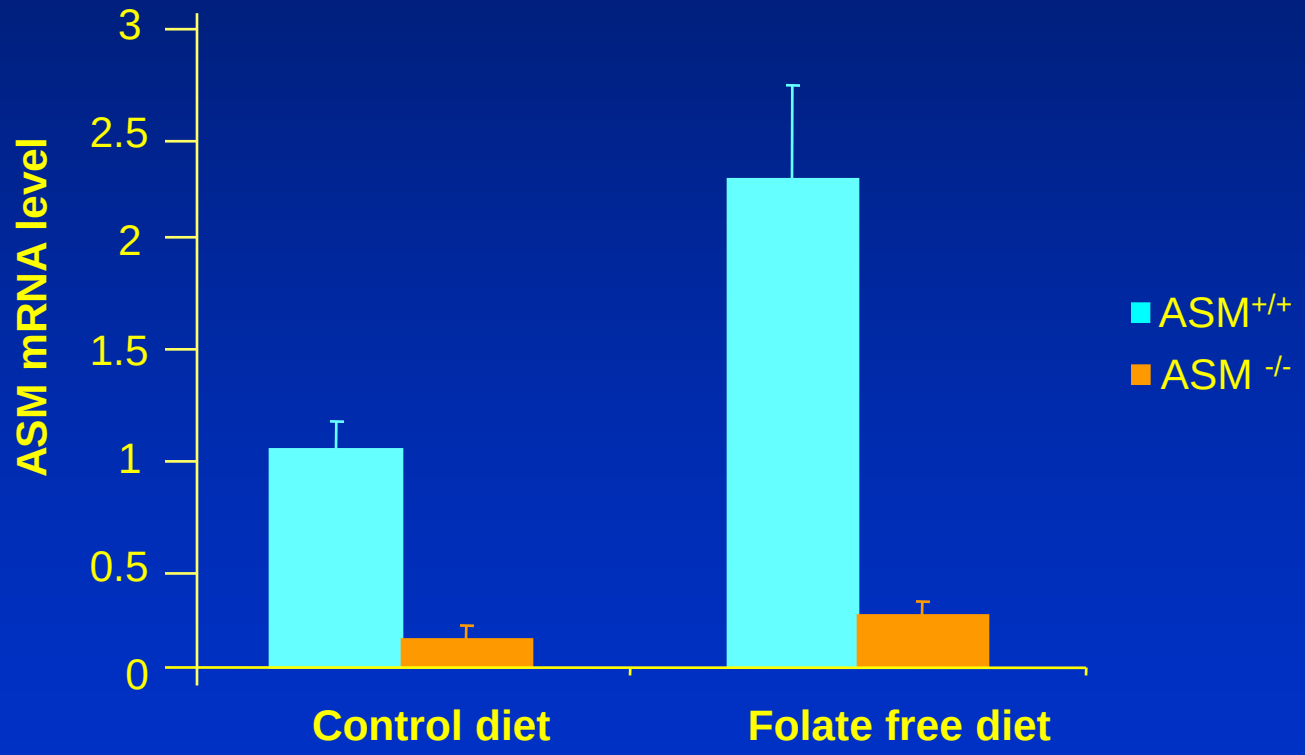
Folate free diet

ASM mRNA level, Plasma Hcy, Urinary protein excretion, Superoxide production and Glomerular injury markers

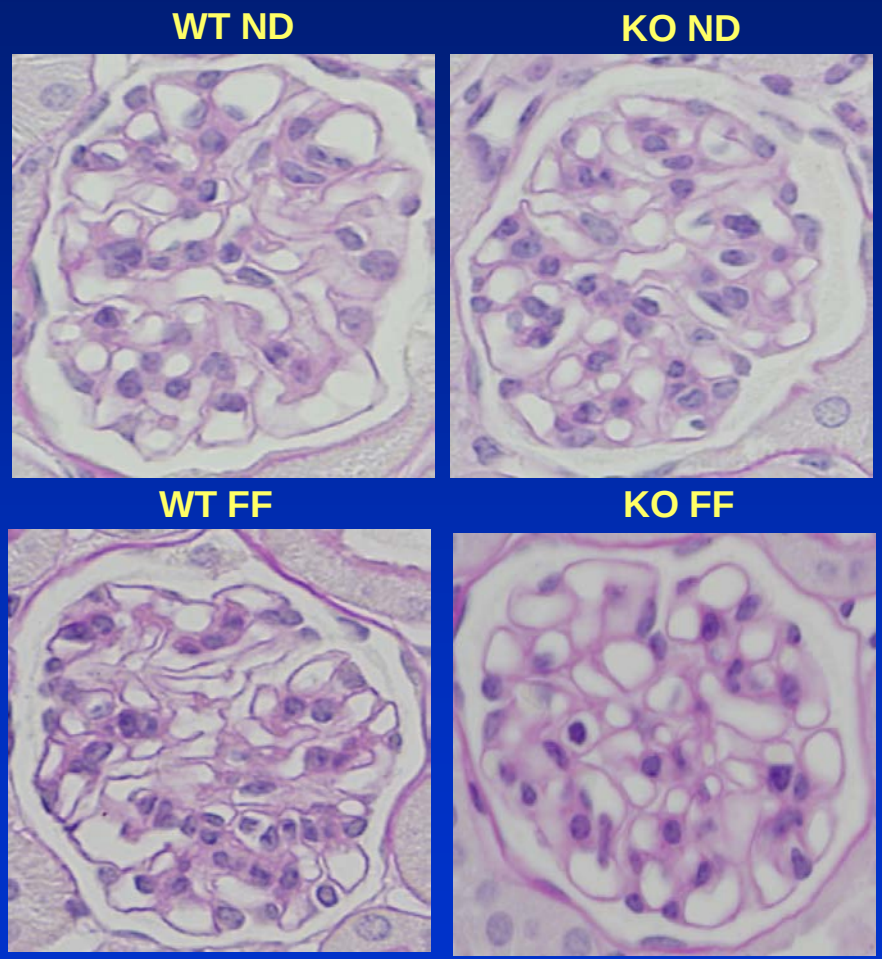
Plasma Hcys concentration in mice

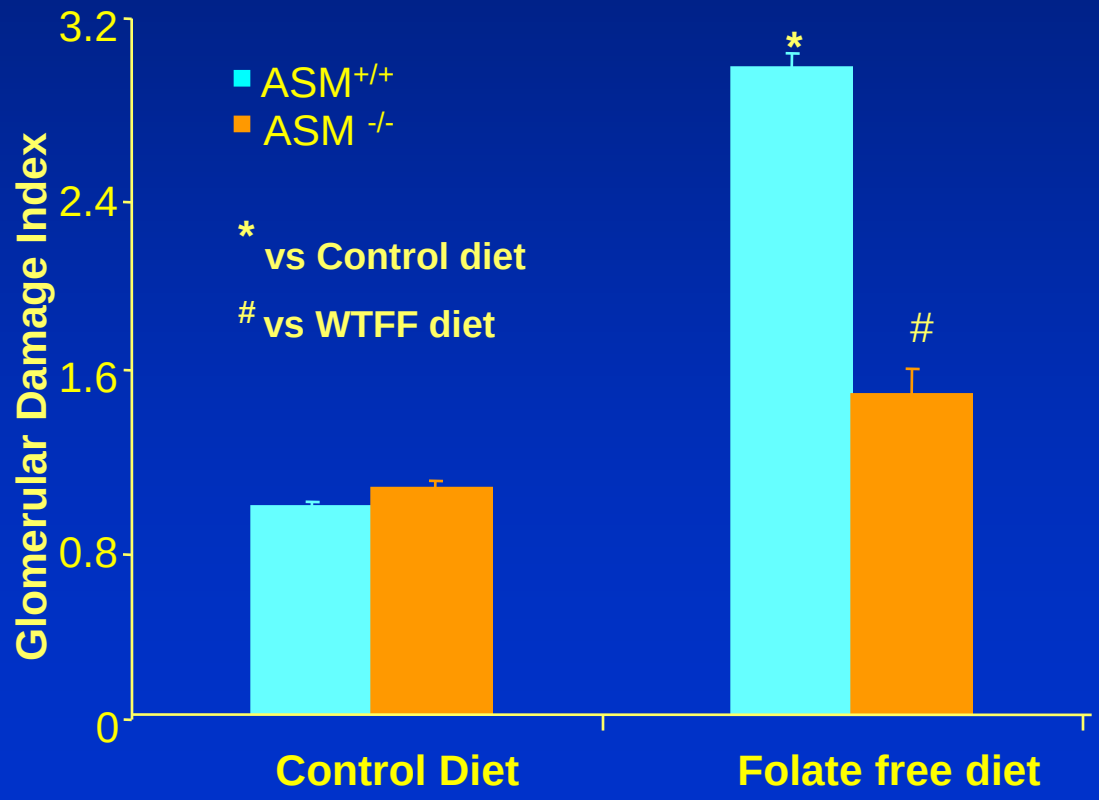


ASM mRNA expression in mice

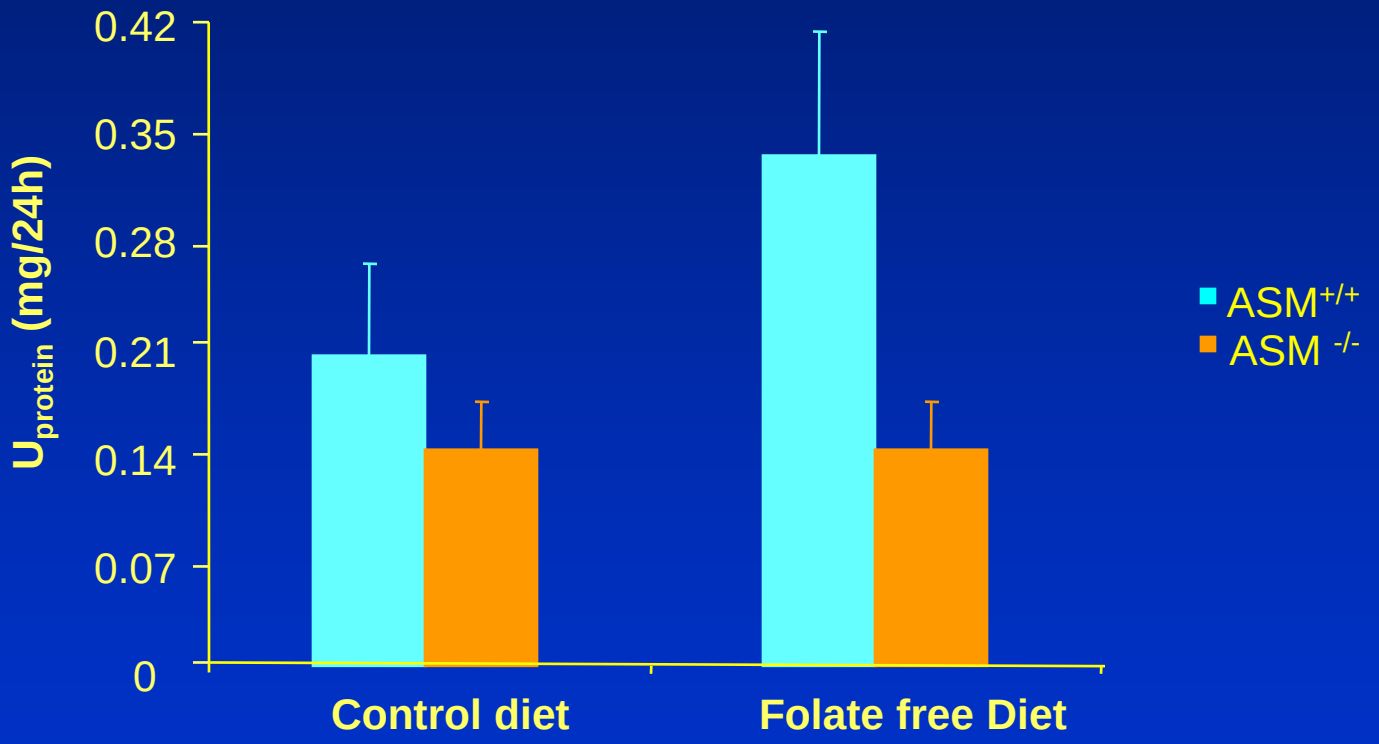


Morphological features of the glomeruli from different groups of mice

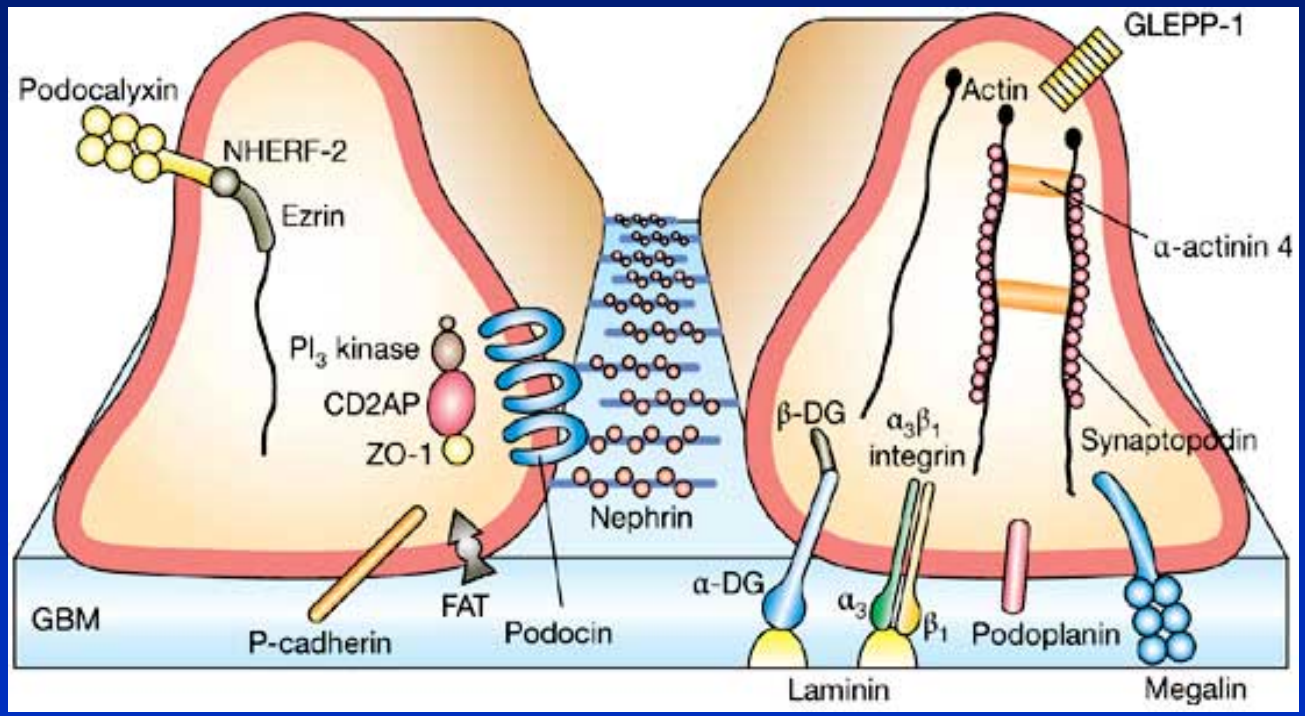




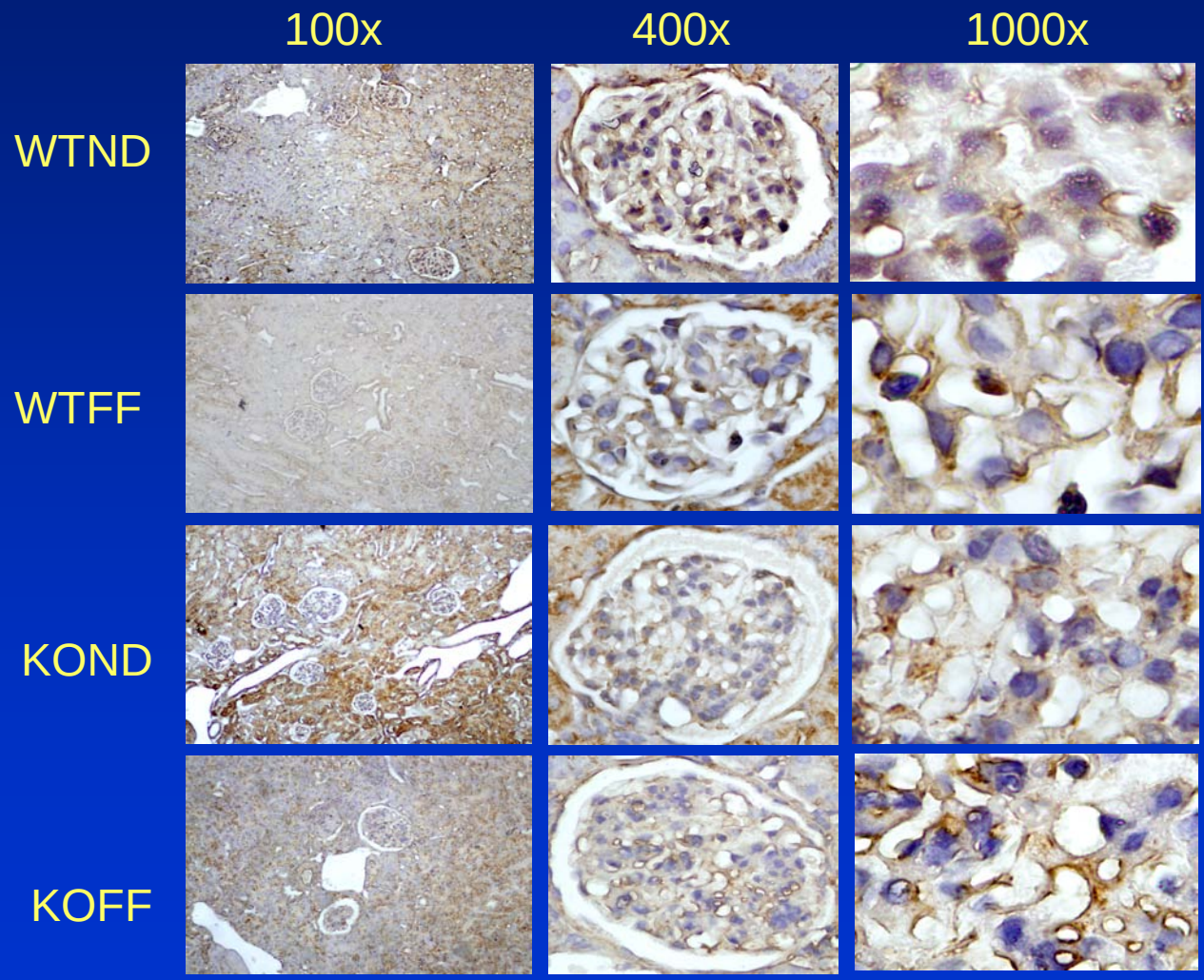
Urinary total protein excretion in mice



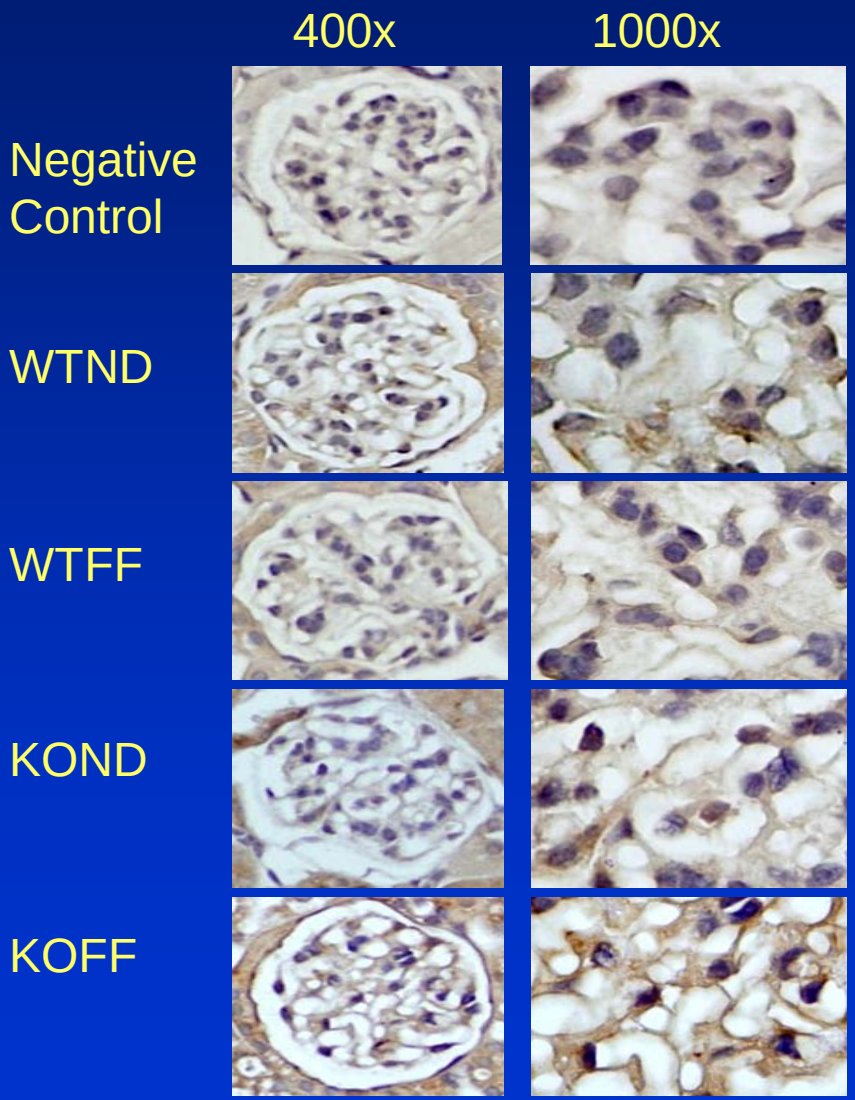
Structure and function of podocytes



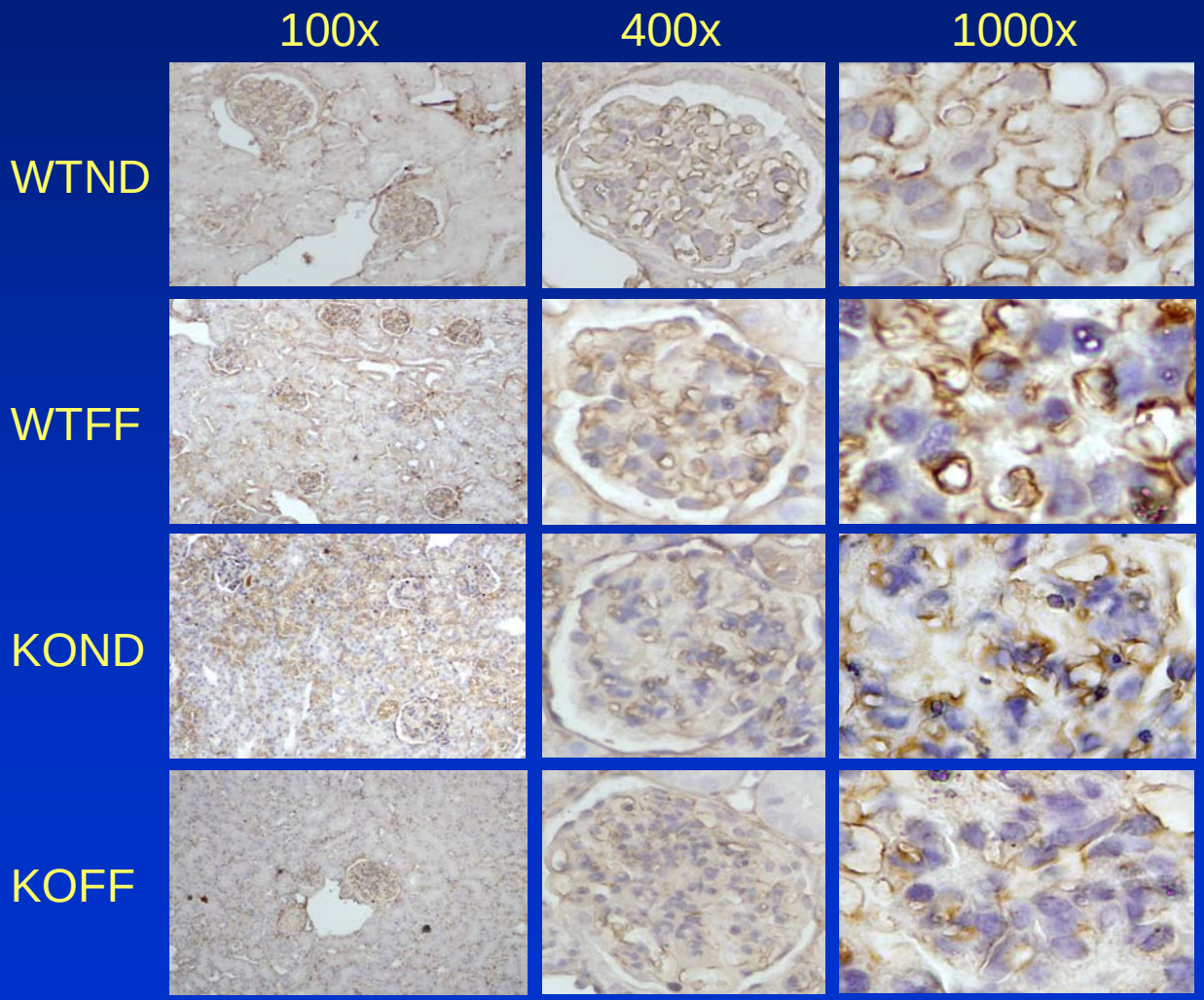
Podocin expression in mice treated with control or folate free diet



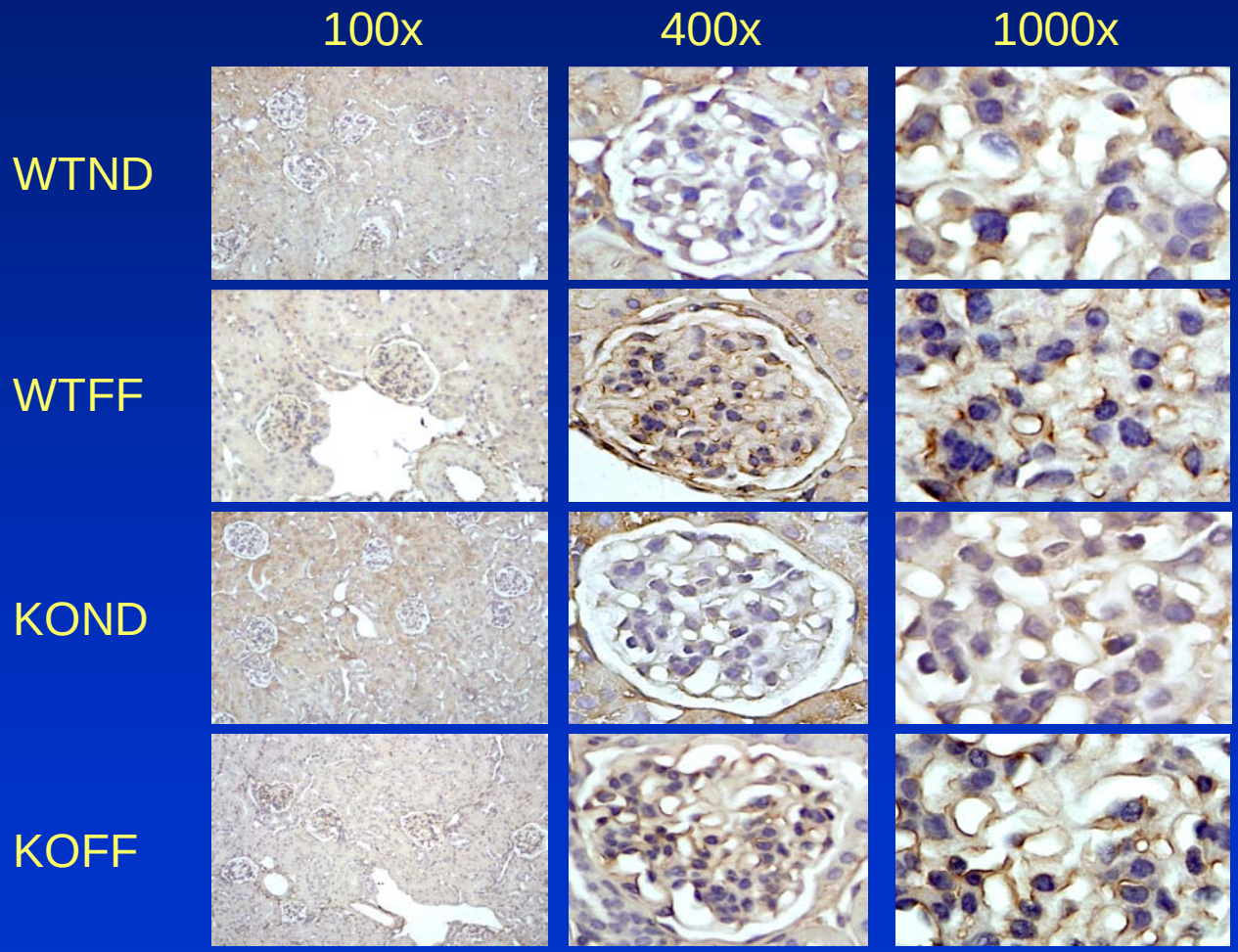
Nephrin expression in mice treated with control or folate free diet



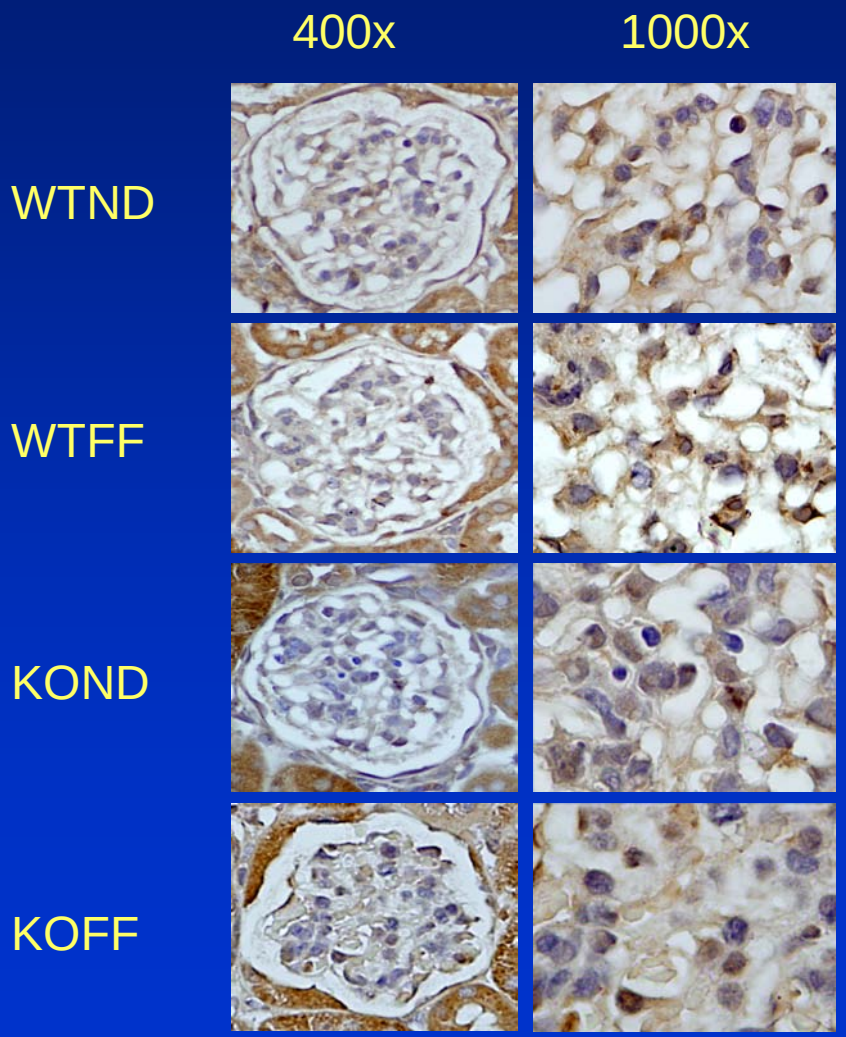
Desmin expression in mice treated with control or folate free diet



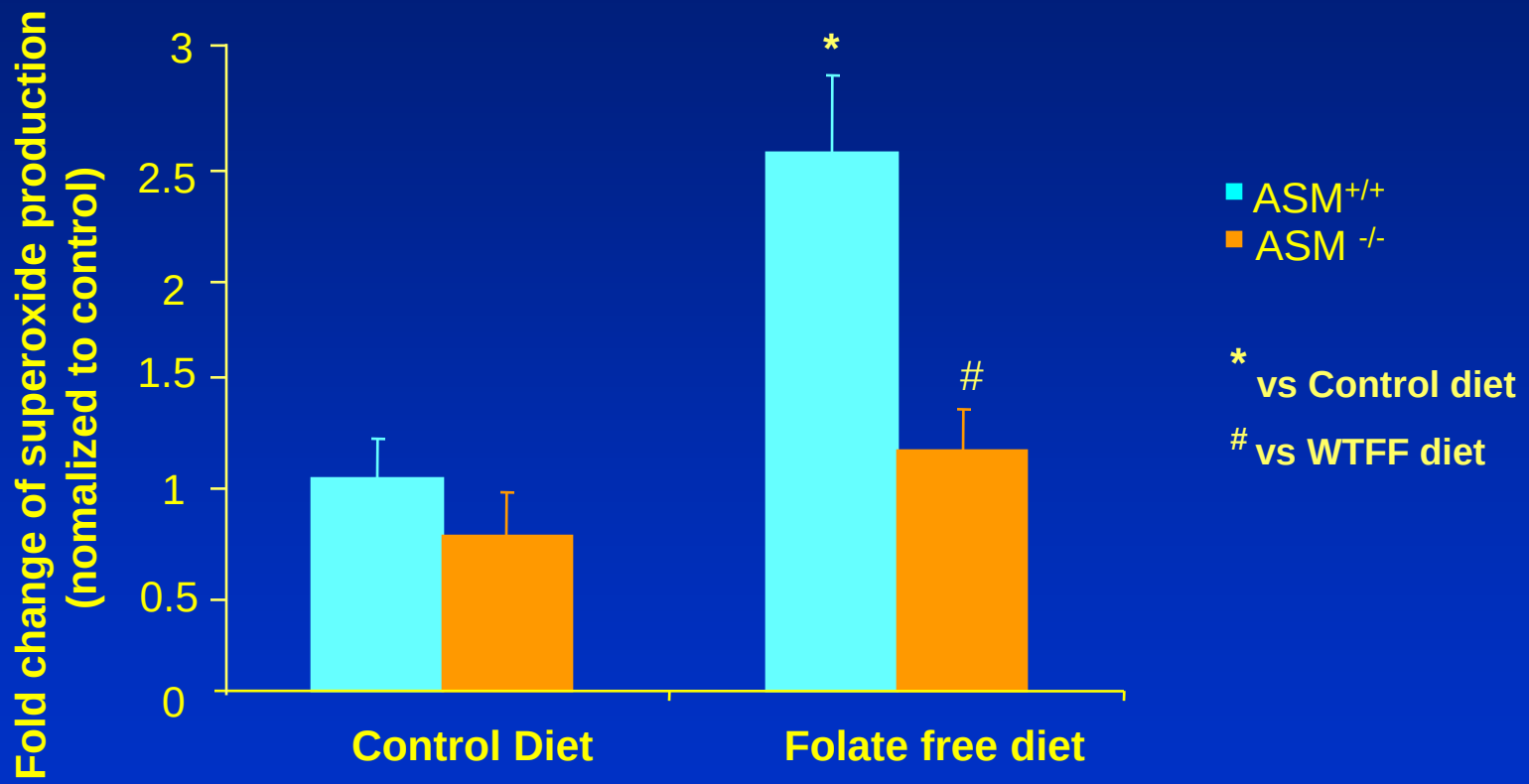
Ceramide expression in mice treated with control or folate free diet



ASM expression in mice treated with control or folate free diet



Superoxide production in ASM mice



Conclusions

Mechanism:

FF Diet- ↑Hcy - ↑ ASM and Ceramide – ↑ LR platform- ↑ Nox/O_2^- - Glomerular injury

Conclusions:

- ASM gene knockout mice attenuates folate free diet induced plasma homocysteine concentration, mRNA level, urinary total protein excretion, and superoxide production compared to the wild type mice.

- ASM gene knockout protects against hyperhomocystenimia induced glomerular injury.

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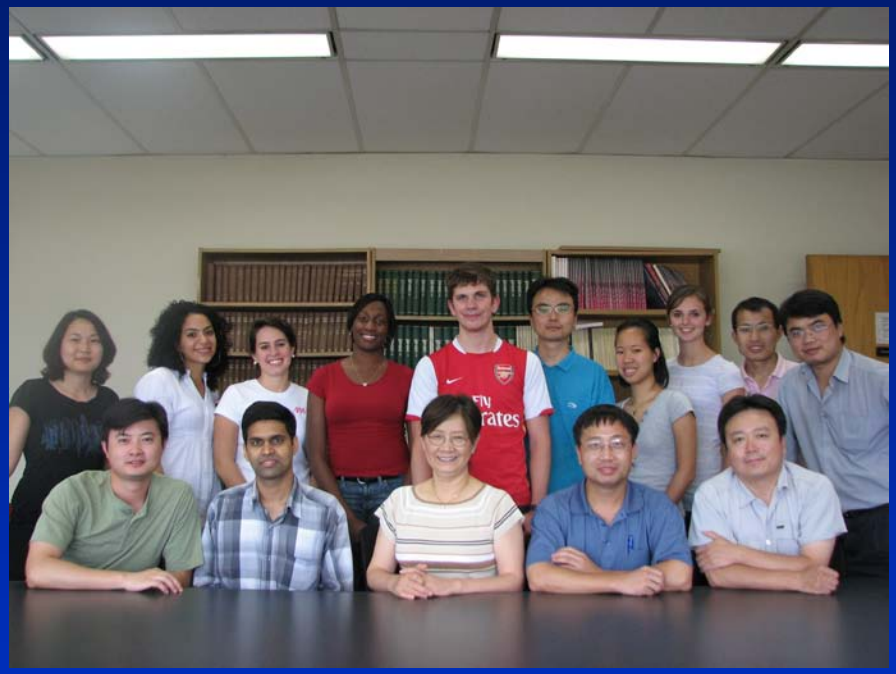

Thank you for everything!